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(21) International Application Number: PCT/US96/00740 (22) International Filing Date: 19 January 1996 (19.01.96) (30) Priority Data: 08/374,422 19 January 1995 (19.01.95) US (60) Parent Application or Grant (63) Related by Continuation US Not furnished (CIP) Filed on Not furnished (71) Applicant (for all designated States except US): CYGNUS, INC. [US/US]; 400 Penobscot Drive, Redwood City, CA 94063 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BESTE, Russell, D. [US/US]; 950 High School Way, #3219, Mountain View, CA 94041 (US). CHIANG, Chia-Ming [US/US]; 380 Shad Court, Foster City, CA 94404 (US). XIA, Jun [-/US]; 450 Vera Avenue, #9, Redwood City, CA 94404 (US).		(74) Agents: KONSKI, Antoinette, F. et al.; Morrison & Foerster L.L.P., 755 Page Mill Road, Palo Alto, CA 94304-1018 (US). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: POLYMER ADHESIVE FORMULATION CONTAINING SORBENT PARTICLES (57) Abstract The cold flow properties of layers of transdermal or transmucosal patches composed of drug/excipient-plasticized polymer adhesives lacking functional groups are maintained at acceptable levels by including a sorptive material in the adhesive-drug/excipient mixture that sorbs a portion of the drug/excipient and thereby prevents the drug/excipient from unduly impairing the cold flow properties of the adhesive.		

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POLYMER ADHESIVE FORMULATION
CONTAINING SORBENT PARTICLES

Cross-Reference to Related Applications

10 This application is a continuation-in-part of
U.S. Serial No. 278,277, filed 21 July 1994, which in
turn is a continuation-in-part of U.S. Serial No.
247,520, filed 23 May 1994, which in turn is a
continuation of U.S. Serial No. 089,971, filed 9 July
15 1993.

Description

Technical Field

20 This invention is in the field of transdermal
drug delivery patches. More particularly, it concerns
adhesive compositions that are used in the patches. The
compositions contain a drug or excipient that plasticizes
the adhesive and thus impairs the cold flow properties of
25 the adhesive and sorbent particles that absorb the
drug/excipient and thereby reduce the plasticization and
cold flow impairment.

Background

30 Most transdermal patches are in the form of a
laminated composite whose basal layer is composed of a
pressure sensitive adhesive layer which either
constitutes the principal drug-containing layer of the
patch or is in-line with the principal drug-containing
35 layer. The term "in-line" means that the adhesive layer

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lies in the diffusional pathway through which the drug travels as it diffuses from the principal drug-containing element of the patch to the skin or mucosa. The principal drug-containing element of the patch is called the "drug-reservoir." In a monolithic type patch, the drug reservoir is typically composed of a matrix of a pressure sensitive polymer adhesive in which the drug and optionally skin permeation enhancer or other excipient is/are dispersed. In a simple monolithic structure, the drug reservoir also serves as the means by which the patch is affixed to the skin or mucosa and defines the basal surface of the patch.

In certain instances, the polymer adhesive component is plasticized or solved by the particular drug or excipient that is being administered. In this regard, the term "excipient" is intended to broadly encompass skin permeation enhancers, solvents and other additives that are intended to alter the skin permeability or release kinetics of the drug from the patch. Depending upon the particular loading of drug/excipient that is required, the adhesive may be plasticized/solved to an extent that the viscosity of the adhesive decreases and its cold flow properties become unacceptable. If this happens, the adhesive composition will ooze out of the patch and make the patch unusable or ineffective.

Particulate materials have been previously added to plasticized polymer adhesives of transdermal patches to increase the cohesive strength of the adhesive and thus improve cold flow. Such materials act as cohesive strengtheners. In this regard, U.S. 4,559,222 discloses the addition of colloidal silicon dioxide to polyisobutylene (PIB) adhesive to increase the viscosity of the PIB and cohesive strength of the PIB. Similarly, EPA 0524776 A1 describes improving the cohesive strength of silicone adhesives that contain functional groups

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(-OH, -COOH) by adding solid strengthening agents which hydrogen bond to the silicone adhesives.

Other references have added solid materials to the polymer adhesives of transdermal patches for purposes other than improving the cold flow properties of the adhesive. For instance, EPA 481,443 A1 discloses using solid microparticles as carriers for the drug. EPA 0224981 and commonly owned copending application U.S. Serial No. 107,323 filed August 16, 1993 teach that the adhesion of hydrophobic adhesives can be maintained by adding materials to the adhesive that will absorb water that migrates into the adhesive from the skin.

Disclosure of the Invention

The present invention is directed to maintaining the cold flow properties of certain polymer adhesives used in transdermal patches that contain plasticizing drugs/excipients in amount(s) that would render the cold flow properties of the adhesive unacceptable. Cold flow properties are maintained by adding sorptive materials to the adhesive that sorb the drug/excipient. The sorbed drug/excipient is thus not free to plasticize the adhesive and impair its cold flow properties. In this invention the sorptive particles act by keeping a portion of the drug/excipient from plasticizing the adhesive rather than as cohesive strengtheners.

Accordingly, one aspect of the invention is a polymer adhesive formulation in the form of a layer of a laminated composite transdermal patch for administering a drug and optionally an excipient, at least one of which is capable of plasticizing the polymer adhesive, said formulation comprising:

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a) a polymer adhesive that is substantially free of functional groups and which, by itself has acceptable cold flow properties;

5 b) said drug and optionally said excipient in an amount sufficient to impair the cold flow properties of the polymer adhesive; and

c) a sorbent material that sorbs a sufficient amount of the drug and/or excipient to maintain the cold flow properties of the adhesive at an acceptable level.

10 Another aspect of the invention is an improvement in a laminated composite transdermal or transmucosal patch having a layer of a polymer adhesive that is substantially free of functional groups and which contains a drug and optionally an excipient, at least one
15 of which is capable of plasticizing the polymer adhesive, in an amount sufficient to impair the cold flow properties of the polymer adhesive. The improvement comprises adding a sorbent material to the polymer adhesive that sorbs a sufficient amount of the
20 drug/excipient to maintain the cold flow properties of the adhesive at an acceptable level.

Still another aspect of the invention is a method for maintaining the cold flow properties of a polymer adhesive at an acceptable level, said polymer
25 adhesive being in the form of a layer of a laminated composite transdermal or transmucosal patch and containing a drug and optionally an excipient, at least one of which is capable of plasticizing the adhesive, in an amount sufficient to impair the cold flow properties
30 of the adhesive, said method comprising including in the adhesive a sorbent material that sorbs a sufficient amount of the drug/excipient to maintain the cold flow properties at said level.

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Modes for Carrying Out the Invention

The adhesive formulations of the invention are used to form a layer of a laminated composite transdermal or transmucosal patch. The layer either constitutes the drug reservoir of the patch or is in line with the drug reservoir. Typically the adhesive formulation layer will define the basal surface of the patch, i.e., the surface that directly contacts the skin or mucosa when the patch is worn.

When the layer constitutes the drug reservoir and defines the basal surface of the patch, the patch will also typically include a backing layer that overlies the adhesive layer. In addition, such patches will typically have a release liner layer that underlies the adhesive layer prior to the time the patch is worn and which is removed from the patch prior to wearing. The composition and structure of backing layers and release liner layers are well known in the art and do not require reiteration herein. The adhesive layer may also include other components, such as non-woven fabric, that are used in the manufacture of the patch.

When the layer does not constitute the drug reservoir, the patch will include a separate drug reservoir. The drug reservoir may be in the form of a matrix (solid or semi-solid layer) or a liquid reservoir formed between other layers of the patch. Such patches will also include a backing layer and release liner layer as described above. They may also include other layers to provide structural support or to control the release rate of drug from the patch. Layers that control the release rate of drug are sometimes referred to as "release rate controlling membranes" in the art.

The polymer adhesive component of the formulation is substantially free of functional groups (e.g., -OH, -COOH, -NH₂) that may interact with the

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sorptive material, such as by hydrogen bonding or covalent bonding. The term "substantially free" means that the quantity of such groups on the polymer, if any, is so low that the sorptive material is not capable of interacting with the polymer adhesive and functioning as a cohesive strengthening agent. Examples of adhesives that are substantially free of functional groups and which are useful in the present invention are amine-resistant polydimethyl siloxanes (silicones), polyisobutylene, block copolymers of polystyrene and polybutadiene/polyisoprene such as certain Kraton, Morstik and Durotak polymers. These adhesives are hydrophobic.

The drugs and excipients that are capable of plasticizing the adhesive polymers are those that are liquid at normal room temperature and act as solvents for the polymers. Examples of such drugs are nicotine, nitroglycerine, benztropine, secovirine, and arecoline. Examples of such excipients are polyethylene glycol monolaurate (PGML), methyl laurate (ML), isopropyl myristate, methyl oleate, 2-hydroxyethyl oleate, and the like. The amount of such drug and/or excipient present in the adhesive formulation is sufficient to impair the cold flow properties of the adhesive in the absence of any other additives. Cold flow properties are also affected by the thickness of the layer. With thinner layers, the minimum acceptable dynamic viscosity is about 10^6 poises as measured with a Rheometrics RMS-800 rheometer at a frequency of 0.001 rad/sec. at 25°C. With thicker layers (e.g., 10 mils) the minimum acceptable dynamic viscosity is in the range of 10^8 poises. Accordingly, depending on the thickness of this layer, the minimum acceptable viscosity will be in the range of about 10^6 to 10^8 poises. The drug will usually constitute 1% to 30% by weight of the adhesive

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formulation, more usually 10% to 20% by weight. When present, the excipient will constitute 1% to 30% by weight of the formulation, more usually 5% to 15% by weight. As indicated, they are present in combined
5 amounts that would plasticize the adhesive in the absence of other additives.

The sorptive materials that are used in the invention are solid and particulate. The particles may be regular or irregular in shape and may be fibrous or
10 nonfibrous. They will normally be porous. Preferably, they are able to sorb about 800% by weight of the sorptive material, normally 100% to 800%. The sorptive material will normally be present in an amount sufficient to sorb about 10% to 50% by weight of the drug/excipient
15 present in the formulation. The sorptive material will usually constitute 5% to 15% by weight of the formulation, more usually 8% to 12% by weight.

Sorptive materials that are useful in the invention have chemical affinity for the drug/excipient
20 and are porous. Examples of such materials are porous silica gel, porous diatomaceous earth such as Celite Micro-cell E, and sorptive nonwoven polymers.

As indicated previously, the sorptive materials do not maintain the cold flow properties of the adhesive
25 by functioning primarily as a cohesive strengthener. Whether a material acts primarily as a cohesive strengthener or primarily by the sorptive mechanism described earlier can be determined by comparing (1) the ratio of the viscosities of pure adhesive with sorptive
30 material to pure adhesive without sorptive material to (2) the ratio of the viscosities of the plasticized adhesive (i.e., adhesive mixed with drug/excipient) with sorptive material to plasticized adhesive without sorptive material. If the quotient of (2) divided by (1)
35 is significantly greater than 1, the material is acting

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primarily by sorption rather than by cohesive strengthening. This quotient is sometimes referred to herein as the viscosity index I. Adhesive formulations of the present invention will normally have a viscosity index greater than about 2. A viscosity index < 1 indicates the material is acting primarily as a cohesive strengthener.

In addition to the adhesive, drug (and optional excipient), and sorptive material, the formulation may also contain tackifiers, dyes, pigments, and other conventional additives that do not deleteriously affect the mechanical or adhesive properties of the formulation. When the drug of the formulation is nicotine, the formulation preferably uses PIB as an adhesive, silica gel as a sorptive material, and a high Tg (i.e., 20°C to 100°C) ESCOREZ[®] resin as a tackifier.

The adhesive compositions of the invention may be formulated by conventional mixing and blending procedures used in the art. Similarly, the patches that include the compositions may be fabricated by conventional prior art procedures. See, for example, U.S. 4,915,950.

The following examples further illustrate the adhesive compositions of the invention and their use. These examples are not intended to limit the invention in any manner.

Example 1

Adhesive formulations were prepared by mixing various adhesives, nicotine/PGML, and various particulate materials. The adhesives were: Dow Corning silicone 4201 (an amine resistant polydimethyl siloxane containing no functional groups); Durotak polymethacrylate 2287 (an uncrosslinked acrylate containing functional groups); Morstik[™] 103 (a polystyrene-polybutadiene block

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copolymer); and polyisobutylene 1:5:2 (a 1:5:2 by weight blend of high molecular weight, low molecular weight, and polybutene). The particulate materials used were: Grace silica gel 63FP; Cabot fumed silica; sodium starch glycolate; and calcium stearate.

Dynamic viscosity (n^*) tests of the pure adhesives with and without particulate material and of the adhesive nicotine/PGML mixtures with and without particulate material were made. The tests were made with a Rheometrics RMS-800 rheometer at a frequency of 0.001 rad/sec at 25°C. The details of these formulations and the results of the viscosity tests are reported in the table below.

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Table I

Adhesive	Particle	Particle Conc.	Pure Adhesive n^* (wp)/ n^* (no p)	Additive	Additive Conc.	Mixture n^* (wp)/ n^* (no p)	Mixture n^* / n^* divided by Adhesive n^* / n^*
4201	Silica Gel 63FP	9.4%	0.4	Nicotine	6.3%	2.7	6.9
4201	Fumed Silica	4.7%	1	Nicotine	6.3%	1.3	1.3
4201	Sodium Starch- Glycolate	4.7%	2	Nicotine	6.3%	0.2	0.1
4201	Prec. Silica Gel	9.4%	0.5	Nicotine	6.3%	0.3	0.6
4201	Calcium Stearate (5% EZ)	10.0%	1.3	PGML	8.0%	1.6	1.2
4201	Silica Gel 63FP	9.4%	0.4	PGML	8.0%	1.1	2.8
4201	Calcium Stearate	9.4%	1	Nicotine	6.3%	0.8	0.8
2287	Silica Gel 63FP	10.0%	1.82	PGML	10.0%	1.50	0.83
M103	Silica Gel 63FP	10.0%	0.09	PGML	8.0%	1.23	13.86
4201	Silica Gel 63FP	10.0%	2.69	ML	10.0%	0.16	0.06
1:5:2	Silica Gel 63FP	15.0%	13.33	Nicotine	4.0%	17.05	1.28

EZ = esradiol

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In the above table, the viscosity index, I, is reported in the last column (mixture n^*/n^* divided by adhesive n^*/n^*). As stated above, indexes in excess of 2 are indicative of significant viscosity increase and thus cold flow improvement effected by the above described sorptive mechanism.

Example 2

A homogeneous mixture of 10% (based on the weight of silica gel plus adhesive) silica gel (WR Grace 63FP) in Dow Corning silicone adhesive 4201 was prepared by mixing appropriate amounts of silica gel and the adhesive plus solvent (heptane) in a rotary mixer for at least two hours. This mixture was coated onto a release liner layer (Scotchpak™ 1022/3M) and a 100% polyester nonwoven fabric (3.4 mg/cm² Veratec Novonette) was laminated onto the adhesive layer and the assembly was dried in an oven at 70°C for 1/2 hr.

The silica gel/adhesive mixture was also coated onto a 0.6 mil thick backing layer (Schüpbach) and the resulting assembly was dried in an oven at 70°C for 1/2 hr.

Nicotine was deposited onto the nonwoven fabric of the release liner/adhesive/fabric assembly in a uniform pattern at 2.8 mg/cm². The backing layer/adhesive assembly was then laminated onto the fabric. The resulting matrix layer (the combined adhesive layers) was 350 microns thick. The laminated composite was cut into 30 cm² pieces, with each piece containing approximately 80 mg nicotine.

Example 3

A homogeneous mixture of 10% (based on the weight of silica gel plus adhesive solids) silica gel (WR Grace 63FP) in Dow Corning Silicone adhesive 4201 was

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prepared using a drive mixer with impeller and shaft. The adhesive mixture is coated onto a release liner layer (Scotchpak™ 1022/3M) by means of a coating knife. The adhesive solvent (heptane) was evaporated in a drying oven with three zones, spending approximately 4.5 minutes in each zone with temperatures set at ambient, 250°C and 300°C. The exposed dried adhesive layer was laminated under uniform roll pressure to the backing film (0.6 mil Schüpbach) to form the backing laminate, or to the nonwoven fabric (3.4 mg/cm² Veratec Novonette) to form the nonwoven laminate. The final dried adhesive weight of each laminate was approximately 20 mg/cm², corresponding to a thickness of 175 microns. After the backing and nonwoven laminates were combined as described below, the total amount of adhesive in the final system was approximately 40 mg/cm², or 350 microns.

Nicotine was applied onto the nonwoven laminate via a fluid delivery system in a uniform pattern at approximately 2.6 mg/cm². The backing laminate was laminated to the nicotine treated nonwoven laminate under uniform roll pressure. Systems (20 cm²) were die-cut from the final laminate using a rotary die. Each final system was placed between two layers of pouch stock (Jefferson Smurfit) and the pouch stock was sealed on all edges.

Example 4

Laminated composites were prepared as in Example 3 except for the following differences. A homogeneous mixture of 15% (based on the weight of silica gel plus adhesive solids) silica gel (WR Grace 63FP) in Dow Corning Silicone adhesive 4201 was prepared. The final dried adhesive weight of each laminate was approximately 15 mg/cm², corresponding to a thickness of 130 microns. After the backing and nonwoven laminates

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were combined, the total amount of adhesive in the final system was approximately 30 mg/cm², or 260 microns. Systems (30 cm²) were die-cut from the final laminate using a rotary die.

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Example 5

Two different sets of prototype transdermal patches were made as follows.

Solutions of HMW PIB (Exxon Vistanex MML-100, M.W. 1,060,000-1,440,000) and LMW PIB (Exxon Vistanex LM-MS-LC, m.w. 42,600-46,100) in hexane were prepared. These solutions were added to silica gel (W.R. Grace Siloid 244FP) wet with hexane and either ESCOREZ[®] 1310LC resin, or ESCOREZ[®] 5300 resin tackifier and blended until the combined mixture was homogeneous. The mixture of HMW PIB, LMW PIB, tackifier (hexane excluded) was in a weight ratio of 2:4:4. The weight ratio of that mixture to silica gel was 90:10.

Each blend was cast onto release liner film (Polyslik 2016, Release International) to a wet thickness of approximately 15 mils and dried. A nonwoven polyester film (Veratech Novonette) was laminated onto one segment of the release liner-adhesive assembly and a polyester backing film (Courtauld 100 gauge) was laminated onto another segment of that assembly. The laminates were die-cut into 20 cm² pieces.

Nicotine was sprayed onto the 20 cm² nonwoven polyester assembly, the release liner was removed from the segment to which the backing layer had been laminated and the two assemblies were laminated together with the adhesive side of the backing layer assembly contacting the nonwoven polyester side of the other assembly. The resulting laminated composite consisted of: the backing layer, a combined adhesive layer in which the nonwoven polyester is imbedded, and a release liner layer. The

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thickness of the combined adhesive layer was 13 mils and it contained a nicotine loading of 2.9 mg/cm².

The adhesive layers of both prototype patches exhibited acceptable cold flow properties.

5 All patents and publications cited heretofore are incorporated herein by reference in their entireties.

10 Modifications of the above-described modes for carrying out the invention that are obvious to persons of skill in the field of transdermal patch fabrication are intended to be within the scope of the following claims.

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Claims

We claim:

- 5 1. A polymer adhesive formulation in the form
of a layer of a laminated composite transdermal or
transmucosal patch for administering a drug and
optionally an excipient, at least one of which is capable
of plasticizing the polymer adhesive, said formulation
10 comprising:
- a) a polymer adhesive that is substantially
free of functional groups and which, by itself has
acceptable cold flow properties;
- b) said drug and optionally said excipient in
15 an amount sufficient to impair the cold flow properties
of the polymer adhesive; and
- c) a sorbent material that sorbs a sufficient
amount of the drug and/or excipient to maintain the cold
flow properties of the adhesive at an acceptable level.
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2. The formulation of claim 1 wherein the
adhesive is a silicone adhesive, a polyisobutylene
adhesive, a polystyrene-polybutadiene adhesive or a
polystyrene-polyisoprene adhesive.
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3. The formulation of claim 2 wherein the
sorptive material is silica gel.
4. The formulation of claim 1 wherein the
30 formulation exhibits a viscosity index above about 2.
5. The formulation of claim 2 wherein said
amount of said drug and optionally said excipient is
sufficient to reduce the dynamic viscosity of the polymer
35 adhesive to below about 10^6 to 10^8 poises.

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6. In a laminated composite transdermal or transmucosal patch having a layer of a polymer adhesive that is substantially free of functional groups and which contains a drug and optionally an excipient at least one of which is capable of plasticizing the polymer adhesive in an amount sufficient to impair the cold flow properties of the polymer adhesive, the improvement comprising adding a sorbent material to the polymer adhesive that sorbs a sufficient amount of the drug/excipient to maintain the cold flow properties of the adhesive at an acceptable level.

7. The patch of claim 6 wherein the adhesive is a silicone adhesive, a polyisobutylene adhesive, a polystyrene-polybutadiene adhesive, or a polystyrene-polyisoprene adhesive.

8. The patch of claim 7 wherein the sorptive material is silica gel.

9. The patch of claim 6 wherein the formulation exhibits a viscosity index above about 2.

10. The patch of claim 6 wherein said amount of said drug and optionally said excipient is sufficient to reduce the dynamic viscosity of the polymer adhesive to below about 10^6 to 10^8 poises.

11. A method for maintaining the cold flow properties of a polymer adhesive at an acceptable level, said polymer adhesive being in the form of a layer of a laminated composite transdermal or transmucosal patch and containing a drug and optionally an excipient, at least one of which is capable of plasticizing the adhesive, in an amount sufficient to impair the cold flow properties

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of the adhesive, said method comprising including in the adhesive a sorbent material that sorbs a sufficient amount of the drug/excipient to maintain the cold flow properties at said level.

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